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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/081,922	02/21/2002	Julianna Lisziewicz	RGT 9771	4590

7590 05/04/2006

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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 05/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/081,922	LISZIEWICZ ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 February 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-26,28,30-33,35 and 37-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-26,28,30-33,35 and 37-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2-21-02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-22, 27, 29, 34 and 36 have been canceled. Claims 23-26, 28, 30-33, 35 and 37-43 remain pending and are under consideration.

The arguments filed 2-6-06 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Priority

This application repeats a substantial portion of prior Application No. 09/153198, filed 9-15-98, and adds additional disclosure in the preliminary amendment that was not in '198. Claim 23 in the preliminary amendment filed in the instant application on 2-21-02 required mixing DNA and "selected from the group consisting of sugars, polyethylenimine, polyethylenimine derivatives, and mixtures thereof" which was not originally disclosed in 09/153,198. Therefore, the instant application is a CIP of '198.

Applicants' response filed 2-21-02 stated the phrase was supported by the original claims; however, the originally claims do not provide support for combining mixtures of sugar, polyethylenimine and polyethylenimine derivatives, with DNA.

The first line will have to be updated to indicate the instant application is a CIP of 09/153198 because '198 did not teach the concept of "mixtures thereof" found in the preliminary amendment filed 2-21-02.

Claims 23-26, 28, 30-33, 35 and 37-43 in the instant application (methods of transfecting APCs using a gene delivery complex) are patentably distinct invention from the claims in parent application 09/153,198, now US Patent 6,240,176, filed 9-15-98 (a gene delivery complex).

Specification

The first line of the specification will have to be updated to indicate the instant application is a CIP of 09/153198. The preliminary amendment filed 2-21-02 claimed "mixtures thereof" of sugars, PEI and PEI derivatives, which was not contemplated in 09/153198.

The status of the application on pg 9, line 7, will have to be updated as necessary.

The status of the application on pg 13, line 36, will need updated as necessary.

The status of the application on pg 18, line 32, will need updated as necessary.

Claim Rejections - 35 USC § 112

New Matter

The limitation of "one or more compounds selected from the group consisting of sugars, polyethylenimine, and polyethylenimine derivatives" in claim 23 has support in the phrase "sugars, polyethylenimine, and polyethylenimine derivatives, and mixtures thereof" in the preliminary amendment on 2-21-02 in claim 23.

Written Description

Claims 23-26, 28, 30-33, 35 and 37-43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention for reasons of record.

The limitation of "one or more compounds selected from the group consisting of sugars, polyethylenimine, and polyethylenimine derivatives" in claim 23 lacks written description. The number of sugars (sucrose, fructose, glucose, galactose, maltose) and the number of PEI derivatives (sucrosylated, glycosylated, mannosylated, as well as any other derivative of PEI) are numerous. Therefore, the phrase encompasses innumerable combinations of sugars, PEI and PEI derivatives.

Claim 23 of the preliminary amendment filed 2-21-02 contemplates using "sugars, polyethylenimine, and polyethylenimine derivatives, and mixtures thereof". However, this is the only place in the specification that describes "one or more compounds" as claimed. Pg 15, lines 6-8, contemplates using PEI, specifically modified PEI, more specifically sugar modified PEI, to target the mannose receptor. Pg 15, lines 6-8, does not teach or suggest using one or more sugar, PEI or PEI derivative as claimed. Pg 15, lines 16-17, teach the mannose receptor size and does not teach or suggest using Example 10 and Table 2 teaches:

"Experimental results depicted in Table 2 provided evidence that a sugar-DNA complex, in the absence of PEI-man, can transduce Langerhans cells in vivo. Sugar complexed DNA in the absence of PEI is more efficient for use in both subcutaneous and transcutaneous methods than DNA complexed with PEI (see Table 2, experiments 3 &

5). This is a very surprising result. It shows that sugars (e.g. 8% glucose in these experiments) can also complex DNA and deliver the DNA to the Langerhans cells via the mannose receptor. Importantly, the most efficient gene delivery in vivo to the Langerhans cells was the sugar complexed DNA used in the transcutaneous way." (pg 24).

Thus, Example 10 describes a sugar-DNA complex in the absence of PEI or PEI-derivates. Table 2 (pg 23) discloses using PEI or mannosylated PEI but does not teach combining PEI or mannyosylated PEI in combination with a sugar solution. Example 10 and Table 2 do not teach or suggest using one or more sugar, PEI or PEI derivative as claimed. Thus, the specification does not provide written description for any specific combination of sugar, PEI and PEI derivatives.

An adequate written description of a combination of elements requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the combinations themselves. It is not sufficient to state a composition comprises one or more sugar, PEI or PEI derivative able to transfect APCs in vivo because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any combination having that biological property. Also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming a method that requires using any combination of sugar, PEI and PEI derivatives that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

Claims 37-39 remain rejected under written description because the specification does not adequately describe how to apply a gene delivery complex encoding an HIV protein to the skin or mucosa of an animal such that a therapeutic or prophylactic immune response against HIV is obtained – the sole disclosed purpose for transfecting APCs disclosed in the specification for reasons of record.

Breadth of the claims

Claims 37-39 require applying a gene delivery complex to the skin or mucosa of an animal, wherein the gene delivery complex comprises DNA encoding a protein from HIV (37), from a replication-defective HIV (38), or an integration-defective, replication-defective HIV (39). The only described function for such a method is to induce an immune response that treats or prevents HIV infection. The specification describes using the method claimed to induce an immune response in a mammal (pg 20, Example 4). Inducing an immune response is only described in the specification as being used to obtain a therapeutic or prophylactic effect (pg 2, lines 20-24; pg 18, lines 2-8). Therefore, the sole purpose for applying a gene complex encoding an HIV protein as claimed must induce an immune response as described in Example 4 and must treat or prevent HIV as described on pg 2, lines 20-24, and pg 18, lines 2-8. While the claims do not require inducing an immune response or treating or preventing HIV, merely applying a gene complex encoding an HIV protein to the skin or mucosa of an animal as claimed, in and of itself, does not have a disclosed use. Accordingly, the specification must provide adequate written description for applying a gene complex encoding an HIV

protein to the skin that induces an immune response capable of treating or preventing HIV.

State of the art and unpredictability of inducing an immune response capable of treating retroviral infection

The state of the art regarding treating retroviral infection was unpredictable. Stricker of record (Medical Hypotheses, June 1997, Vol. 48, pages 527-9) taught that attempts to develop a vaccine against HIV have been unsuccessful because HIV vaccines do not neutralize HIV (pg 527, last paragraph through all of pg 528). Overall, a lack of understanding about protective immunity to HIV in humans, the sequence variability of HIV and the rapid replication of HIV contribute the ineffectiveness of vaccines against HIV (Bangham of record, Nov. 29, 1997, Lancet, Vol. 350, pages 1617-1621; page 1617, top of col. 1).

More specifically, Veljkovic (Vaccine, 2001, Vol. 19, pg 1855-1862) taught:

> "As was recently reported, the rgp120 subunit vaccine tested in HIV-negative individuals was not only not effective — participants in Phase I:II clinical vaccine trials who have become infected during or following immunization with the HIV-1 env had in their sera significant neutralizing antibody titers against vaccine isolates before they became infected [2,3] — but could also be dangerous [4]." (pg 1856, col. 1, first sentence of the second full paragraph)

Thus, the immune response against an HIV gp120 vaccine is inadequate to provide a prophylactic or therapeutic effect against HIV infection.

In fact, Veljkovic taught HIV could escape recognition by HIV-specific CTL because the virus undergoes mutation within weeks after infection (pg 1857, col. 1, last sentence of the first full paragraph). McMichael explicitly described this phenomenon (Annual Rev. Immunol., 1997, Vol. 15, pg 27-296; see entire article).

Hanke (Immunology Letters, 1999, Vol. 66, pg 177-181) taught administering DNA encoding HIV proteins intradermally caused a CTL response (pg 178, section 2.1). Hanke did not teach the CTL response was therapeutic or prophylactic. Hanke asks the question whether inducing a CTL response can protect against HIV infection and states "CTL per se cannot prevent incoming cell-free virus from infecting host T-cells. However, if there are high levels of memory CTL present in the relevant tissue or circulation and the virus 'challenge" is low, CTL might clear the small number of infected cells before the virus spreads further and establishes generalized infection" (pg 180, col. 1, Section 4.2).

Weber (Eur. J. Clin. Microbiol. Infect. Dis., Nov. 2001, Vol. 20, pg 800-803) described the phase I clinical trial using plasmid encoding HIV-1 gp160 to treat HIV-infected humans. "Even though both trials were designed as phase I clinical trials, with special focus on safety, preliminary data suggest that vaccination with the present HIV-1 DNA construct did not show any virological or immunological efficacy, which is in contrast to findings in the chimpanzee model" (pg 802, col. 2, first sentence of first full paragraph). Thus, plasmid DNA encoding gp160 does not have a therapeutic effect in humans and using DNA encoding HIV proteins in primate models does not correlate to expected results in humans.

Ready (Nature Medicine, (April 2003, Vol. 9, No. 4, pg 376) clearly states that HIV vaccines capable of preventing infections in humans was not predictable (col. 1, last full ¶) and that the road to such a vaccine "is littered with abandoned candidates" (col. 1, last 4 lines). For example, a canarypox vaccine failed induce a powerful enough

immune response (sentence bridging columns 1 and 2). In another trial, three or four monkeys treated with a promising DNA vaccine have died due to viral breakthrough (column 2, first full sentence).

Lori (Current Medical and Chemical Anti-Infective Agents, 2004, Vol. 3, pg 31-41) taught that inducing an HIV-specific immune response in vivo against HIV protein fails to provide a therapeutic or prophylactic effect (pg 31, col. 1, 2nd ¶, lines 7-10).

Dong (J. Exp. Med., Dec. 20, 2004, Vol. 200, No. 12, pg 1547-1557) taught, "HIV-specific cytotoxic T lymphocytes (CTL) are important in controlling HIV replication, but the magnitude of the CTL response does not predict clinical outcome" (first sentence of abstract, emphasis added). The CTL response generated against HIV-1 proteins has no correlation with either the magnitude/breadth of the response or the plasma viral load (pg 1547, col. 2, first full sentence). In other words, obtaining a CTL response against HIV proteins does not predict the clinical response.

Teachings in the specification

Applicants taught using the LW/int- plasmid encoding replication-defective, integrase-defective retroviral DNA in the claimed invention (pg 13, lines 26-37; described in related application 08/803,484).

Example 4 teaches transfecting dendritic cells in vitro with the LW/Int- plasmid and injecting the dendritic cells into monkeys (split subcutaneously and intravenously). One monkey showed a CTL response (pg 20, lines 8-19).

Example 9 teaches applying a gene delivery complex encoding GFP to the skin of mice. GFP was expressed in dendritic cells.

The specification described plasmids encoding replication defective, integrase-defective HIV as described in application 08/989,301 (pg 18, line 30-32). In application 08/939,301, applicants call such retroviruses "Class 4" viruses that are infectious but replication-defective (pg 15, lines 1-5). In application '301, applicants teach that replication-defective HIV may fail to elicit a prophylactic immune response because it fails to replicate at all; however, replication-defective HIV may cause HIV because it replicates albeit poorly (pg 3, line 17 through pg 4, line 3). Application '301 describes applicants' attempted to find a vector encoding a replication-defective HIV that replicated poorly so that it would elicit a prophylactic immune response without causing HIV syndrome. '301 taught numerous HIV vectors that had decreased replication and some that induced an immune response against HIV, but '301 did not teach any HIV vectors that induced a therapeutic or prophylactic immune response against HIV.

Rejection

The specification does not provide adequate written description for applying a gene delivery complex encoding an HIV protein to the skin or mucosa of an animal such that a therapeutic or prophylactic immune response is obtained.

Example 4 does not correlate to the claimed invention because dendritic cells were transfected in vitro and because the gene delivery complex was not applied to the skin or mucosa as claimed. Furthermore, merely inducing a CTL in one monkey by administering transfected dendritic cells as described in Example 4 is not statistically significant; the observed CTL response may have been a random event and not caused by the administration of dendritic cells. Finally, inducing a CTL response against HIV in

vivo as described in Example 4 is not adequate to treat or prevent HIV infection. According to Weber (cited above), DNA encoding HIV proteins may induce an immune response without treating or preventing HIV. Nowhere have applicants provided any evidence that the CTL response observed is adequate to treat or prevent HIV or that the virus does not replicate too much and cause disease. As such, use of DNA encoding HIV proteins as described in Example 4 would not treat or prevent disease because the virus would replicate and cause disease and because the CTL response observed is inadequate to overcome HIV infection.

Example 9, pg 23-24, does not correlate to the invention as now claimed because it does not disclose delivering DNA encoding HIV proteins to the skin, inducing an immune response against the proteins, specifically a therapeutic or prophylactic immune response.

Applicants appear to be attempting to find how to apply DNA encoding an HIV protein to the skin or mucosa of an animal such that a therapeutic or prophylactic immune response is obtained. Claiming a method that may exist, in the absence of knowledge as to the specific structure of the material used or the specific route of administration, dosage and immune response required to treat or prevent disease, is not a description of that method. Thus, claiming a method of using DNA encoding replication-defective retroviral proteins without defining the parameters required to induce an immune response that is therapeutic/prophylactic, i.e. the combination of PEI, sugars and PEI derivatives, specific route of administration, dosage or immune response required to treat or prevent HIV is not in compliance with the description

requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

Applicants' arguments

Applicants argue the language was approved in the parent application; therefore, applicants conclude the language has written description. Applicants' argument is not persuasive. The parent application claims a gene delivery complex while the instant claims require applying a gene delivery complex comprising DNA encoding an HIV protein and sugars, PEI, PEI derivatives or mixtures thereof to the skin of an animal. The instant application lacks written description for treating or preventing HIV using the methods of claims 37-39, the sole disclosed use of the methods of claims 37-39. The gene delivery complex claimed in the parent application was not solely used to treat or prevent HIV.

Applicants argue the claimed material was used in an experiment that resulted in a therapeutic effect on pg 20, Example 4. Applicants' argument is not persuasive. Example 4 does not use the claimed material; Example 4 injected dendritic cells transfected in vitro while the claims require applying a gene delivery complex to the skin or mucosa of an animal. Furthermore, obtaining a CTL response against HIV as taught in Example 4 is not predictive of the clinical outcome (Dong cited above). Accordingly, Example 4 does not correlate to the claims and does not provide a reasonable explanation that the CTL response observed would cause a therapeutic outcome.

Applicants point to Example 9, pg 23-24, which describes applying a gene complex to the skin of an animal. Applicants conclude claims 37-39 have written description because Example 9 shows a gene complex applied to the skin transfected dendritic cells. Applicants' argument is not persuasive. It is noted that Examples 8 and 9 do not teach how the DNA was applied to the skin of the mice (i.e. topically or intradermally), which may be essential to the invention. More importantly, Example 9 does not disclose delivering DNA encoding HIV proteins, or inducing a CTL response, specifically a therapeutic or prophylactic response. Thus, Example 9 does not provide correlate to the claims and does not teach treating or preventing HIV.

Applicants argue Lisziewicz (J. Invest. Derm.) details the use of the present invention to produce a CTL response. It is noted that Lisziewicz (2004) provided by applicants appears to be a copy of the article from the publisher. The correct citation for the article is J. Invest. Derm., Jan. 2005, Vol. 124, No. 1, pg 160-169, hereby referred to as Lisziewicz (2005).

Applicants argument is not persuasive because the specific combination of DNA, PEI-mannose and glucose described by Lisziewicz (2005) does not have written description in the specification as originally filed, because the narrow limitation of applying DNA, PEI-mannose and glucose topically as described by Lisziewicz (2005) does not provide adequate written description for the claim as broadly written and because Lisziewicz (2005) did not teach the CTL response was therapeutic or prophylactic.

Lisziewicz (2005) taught using DermaVir to make particles containing DNA, PEIm and glucose and administering the complex on about 40 cm2 skin at four locations: the left and right upper inguinal region and left and right axillary region for 30 minutes (pg 167, col. 1, "Topical and *ex vivo* DermaVir immunization"). The structure of DermaVir is described as being "formulated to make a approximately 100 nm particle containing DNA, PEIm, and glucose" (pg 167, col. 1, "Topical and *ex vivo* DermaVir Immunization" of Lisziewicz (2005)). The specific structure of DermaVir is not described. Furthermore, the combination of DNA, PEIm and glucose described by Lisziewicz (2005) does not have written description in the instant specification. While the preliminary amendment contemplates using sugars, PEI, PEI derivatives or mixtures thereof (claim 23), the specification as originally filed does not contemplate the specific combination of DNA, PEI-mannose and glucose. Given the innumerable combinations of sugars, PEI and PEI derivatives, the specification as originally filed does not reasonably lead those of skill to the conclusion that applicants contemplated the specific combination of DNA, PEI-mannose and glucose as described by Lisziewicz (2005). Accordingly, the teachings of Lisziewicz (2005) cannot be relied upon for written description.

Furthermore, Lisziewicz (2005) is limited to gene delivery particles containing plasmid DNA, PEI-mannose and glucose applied topically (pg 166, col. 2, 1st full ¶), which cannot be relied upon for written description of the gene delivery complex as broadly claimed or to applying the complex to the skin or mucosa as broadly claimed.

Finally, Lisziewicz (2005) induced CD4 helper and CD8 cells but did not obtain a therapeutic or prophylactic effect against HIV. However, Ready (Nature Medicine, (April

2003, Vol. 9, No. 4, pg 376) clearly states that HIV vaccines capable of preventing infections in humans was not predictable (col. 1, last full ¶) and that the road to such a vaccine "is littered with abandoned candidates" (col. 1, last 4 lines). Furthermore, obtaining a CTL response against HIV as taught in Lisziewicz (2005) is not predictive of the clinical outcome (Dong cited above). Finally, Lori (Current Medical and Chemical Anti-Infective Agents, 2004, Vol. 3, pg 31-41), one of the inventors in the instant application, taught that inducing HIV-specific antibodies failed to provide a protective effect (pg 31, col. 1, 2nd ¶, lines 7-10). Lori also says inducing a cellular immune response will not prevent HIV infection (pg 31, col. 2, first sentence of the new paragraph). While Lori suggests a cellular immune response may treat HIV in the same sentence, Lori does not teach the CTL response required to do so. Applicants have not provided any evidence or any reasonable expectation that CD4 and CD8 cells that recognize HIV proteins overcomes such unpredictability so that a therapeutic or prophylactic effect would be obtained. Without such guidance, merely inducing CD4 helper and CD8 cells that recognize HIV proteins as described by Lisziewicz (2005) is not adequate written description for inducing an immune response against HIV proteins that is therapeutic or prophylactic.

As such, Lisziewicz (2005) cannot be relied upon for written description of the instant application because it required combining DNA, PEIm and glucose, which does not have written description in the instant application, because neither the instant application or Lisziewicz (2005) disclose the structure of DermaVir and because

inducing a CD4 and CD8 response against HIV does not induce a therapeutic or prophylactic effect against HIV.

Applicants' arguments on pg 10 titled "Fine-tuned DNA" are noted; however, the arguments are not persuasive. The examiner has not required any fine-tuning of gene complexes disclosed in the specification or known in the art. The examiner has required a reasonable written description of a gene complex that will induce a therapeutic or prophylactic immune response against HIV upon being administered to the skin as claimed.

Applicants argue Lisziewicz (2001, J. Virol., Aug. 2001, Vol. 75, No. 16, pg 7621-7628) provides written description for treating or preventing HIV using DNA encoding HIV proteins as claimed. Applicants' argument is not persuasive. Lisziewicz (2001) transfected dendritic cells with a vector encoding HIV proteins, injected them subcutaneously into monkeys and obtained a CTL response against HIV (pg 7622, col. 2, first two paragraphs; pg 7625, Fig. 6b). First, Lisziewicz (2001) does not correlate to the claims because the gene delivery complex was not applied to the skin or mucosa as claimed. Second, the vector used by Lisziewicz (2001) was not described in the specification as originally filed. The vector used by Lisziewicz (2001) has six stop codons, one deletion in the pol region, one stop codon and one deletion in the second reading frame and is integrase negative (pg 7621, col. 2). While pg 18, line 31, of the instant application mentions the LWint- vector of application 08/803484, the LWint- vector does not have six stop codons, one deletion in the pol region, one stop codon and one deletion in the second reading frame and is integrase negative. Therefore, the

vector in Lisziewicz (2001) does not have written description in the specification as originally filed. Third, Lisziewicz (2001) did not obtain a CTL response capable of treating or preventing HIV. The art taught that inducing an HIV-specific immune response in vivo against HIV protein failed to provide a therapeutic or prophylactic effect (Lori, Current Medical and Chemical Anti-Infective Agents, 2004, Vol. 3, pg 31-41; pg 31, col. 1, 2nd ¶, lines 7-10). Ready (Nature Medicine, (April 2003, Vol. 9, No. 4, pg 376) clearly states that HIV vaccines capable of preventing infections in humans was not predictable (col. 1, last full ¶) and that the road to such a vaccine "is littered with abandoned candidates" (col. 1, last 4 lines). Applicants have not provided any evidence or any reasonable explanation that the CTL response against HIV obtained in Lisziewicz (2001) overcomes such unpredictability so that a therapeutic or prophylactic effect would be obtained. Without such guidance, inducing a CTL response against HIV in vivo as described by Lisziewicz (2001) is not adequate written description for inducing a therapeutic or prophylactic CTL response against HIV in vivo.

It is noted that Lisziewicz (2005) states DermaVir was used in Lisziewicz (2001, of record); however, Lisziewicz (2001) does not discuss using DermaVir. Lisziewicz (2001) described using PEI or PEI-mannose to deliver DNA (at a 5:1 ratio) without using glucose. The gene delivery complex used in Lisziewicz (2005) is different than the one used in Lisziewicz (2001).

Enablement

The rejection of claims 23-26, 28, 30-33, 35 and 40-42 regarding obtaining a therapeutic effect by applying a gene delivery complex encoding at least one immunogenic antigen to the skin or mucosa of an animal was withdrawn in the office action of 10-5-05.

Claims 37-39 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record.

Claims 37-39 are not enabled because the specification does not provide adequate guidance for one of skill to induce a therapeutic or prophylactic immune response by applying a gene delivery complex encoding HIV to the skin or mucosa of an animal.

Breadth of the claims

Claims 37-39 require applying a gene delivery complex that targets APCs to the skin or mucosa of an animal, wherein the complex comprises i) DNA encoding an immunogenic protein operably linked to a promoter; and one or more compounds selected from the group consisting of sugars, polyethylenimine (PEI), and PEI derivatives, wherein the protein is from HIV (37), a replication-defective HIV (38), or an integration-defective, replication-defective HIV (39).

The specification describes using the method claimed to induce an immune response in a mammal (pg 20, Example 4). However, merely inducing an immune response in a mammal, in and of itself, does not have an enabled use because inducing an immune response is only described in the specification as being used to obtain a therapeutic or prophylactic effect (pg 2, lines 20-24; pg 18, lines 2-8). Therefore, inducing an immune response against HIV according to the specification must result in a therapeutic or prophylactic effect to have an enabled use. The ordinary artisan reading claims 37-39 in view of the specification would determine that the immune response against HIV protein must be therapeutic or prophylactic. The enablement rejection b) is based on the sole disclosed use for the methods of claims 37-39 – inducing an immune response against HIV that is therapeutic or prophylactic.

State of the art and unpredictability of inducing an immune response capable of treating retroviral infection

The state of the art regarding treating retroviral infection was unpredictable. Stricker of record (Medical Hypotheses, June 1997, Vol. 48, pages 527-9) teaches that attempts to develop a vaccine against HIV have been unsuccessful because HIV vaccines do not neutralize HIV (pg 527, last paragraph through all of pg 528). Overall, a lack of understanding about protective immunity to HIV in humans, the sequence variability of HIV and the rapid replication of HIV contribute the ineffectiveness of vaccines against HIV (Bangham of record, Nov. 29, 1997, Lancet, Vol. 350, pages 1617-1621; page 1617, top of col. 1).

More specifically, Veljkovic (Vaccine, 2001, Vol. 19, pg 1855-1862) taught:

> "As was recently reported, the rgp120 subunit vaccine tested in HIV-negative individuals was not only not effective — participants in Phase I:II clinical vaccine trials who have become infected during or following immunization with the HIV-1 env had in their sera significant neutralizing antibody titers against vaccine isolates before they became infected [2,3] — but could also be dangerous [4]." (pg 1856, col. 1, first sentence of the second full paragraph)

Thus, the immune response against an HIV gp120 vaccine is inadequate to provide a prophylactic or therapeutic effect against HIV infection.

In fact, Veljkovic taught HIV could escape recognition by HIV-specific CTL because the virus undergoes mutation within weeks after infection (pg 1857, col. 1, last sentence of the first full paragraph). McMichael explicitly described this phenomenon (Annual Rev. Immunol., 1997, Vol. 15, pg 27-296; see entire article).

Hanke (Immunology Letters, 1999, Vol. 66, pg 177-181) taught administering DNA encoding HIV proteins intradermally caused a CTL response (pg 178, section 2.1). Hanke did not teach the CTL response was therapeutic or prophylactic. Hanke asks the question whether inducing a CTL response can protect against HIV infection and states "CTL per se cannot prevent incoming cell-free virus from infecting host T-cells. However, if there are high levels of memory CTL present in the relevant tissue or circulation and the virus 'challenge" is low, CTL might clear the small number of infected cells before the virus spreads further and establishes generalized infection" (pg 180, col. 1, Section 4.2).

Weber (Eur. J. Clin. Microbiol. Infect. Dis., Nov. 2001, Vol. 20, pg 800-803) described the phase I clinical trial using plasmid encoding HIV-1 gp160 to treat HIV-infected humans. "Even though both trials were designed as phase I clinical trials, with special focus on safety, preliminary data suggest that vaccination with the present HIV-1

DNA construct did not show any virological or immunological efficacy, which is in contrast to findings in the chimpanzee model" (pg 802, col. 2, first sentence of first full paragraph). Thus, plasmid DNA encoding gp160 does not have a therapeutic effect in humans and using DNA encoding HIV proteins in primate models does not correlate to expected results in humans.

Ready (Nature Medicine, (April 2003, Vol. 9, No. 4, pg 376) clearly states that HIV vaccines capable of preventing infections in humans was not predictable (col. 1, last full ¶) and that the road to such a vaccine "is littered with abandoned candidates" (col. 1, last 4 lines). For example, a canarypox vaccine failed to induce a powerful enough immune response (sentence bridging columns 1 and 2). In another trial, three or four monkeys treated with a promising DNA vaccine have died due to viral breakthrough (column 2, first full sentence).

Lori (Current Medical and Chemical Anti-Infective Agents, 2004, Vol. 3, pg 31-41) taught that inducing an HIV-specific immune response in vivo against HIV protein fails to provide a therapeutic or prophylactic effect (pg 31, col. 1, 2nd ¶, lines 7-10).

Dong (J. Exp. Med., Dec. 20, 2004, Vol. 200, No. 12, pg 1547-1557) taught, "HIV-specific cytotoxic T lymphocytes (CTL) are important in controlling HIV replication, but the magnitude of the CTL response does not predict clinical outcome" (first sentence of abstract, emphasis added). The CTL response generated against HIV-1 proteins has no correlation with either the magnitude/breadth of the response or the plasma viral load (pg 1547, col. 2, first full sentence). In other words, obtaining a CTL response against HIV proteins does not predict the clinical response.

Teachings in the specification

Applicants taught using the LW/int- plasmid encoding replication-defective, integrase-defective retroviral DNA in the claimed invention ((pg 13, lines26-37), described in related application 08/803,484).

Example 4 teaches transfecting dendritic cells in vitro with the LW/Int- plasmid and injecting the dendritic cells into monkeys (split subcutaneously and intravenously). One monkey showed a CTL response (pg 20, lines 8-19).

Example 9 teaches applying a gene delivery complex encoding GFP to the skin of mice. GFP was expressed in dendritic cells.

The specification teaches making plasmids encoding replication defective, integrase-defective HIV as described in application 08/989,301 (pg 18, line 30-32). In application 08/939,301, applicants call such retroviruses "Class 4" viruses that are infectious but replication-defective (pg 15, lines 1-5). In application '301, applicants teach that a replication defective HIV that fails to replicate effectively is inadequate to elicit a protective cellular immune response. On the other hand, a replication defective HIV will still cause HIV (pg 3, line 17 through pg 4, line 3). Therefore, applicants' idea was to find an HIV vector that had enough infectivity/replication to induce a therapeutic immune response against HIV without causing HIV syndrome. '301 taught numerous HIV vectors that had decreased replication and some that induced an immune response against HIV, but '301 did not teach any HIV vectors that induced a therapeutic or prophylactic immune response against HIV or any HIV vectors that had enough

infectivity/replication to induce a therapeutic immune response against HIV without causing HIV syndrome.

Rejection

Example 4 does not correlate to the claimed invention because dendritic cells were transfected in vitro and because the gene delivery complex was not applied to the skin or mucosa as claimed. Furthermore, merely inducing a CTL in one monkey by administering transfected dendritic cells as described in Example 4 is not statistically significant; the observed CTL response may have been a random event and not caused by the administration of dendritic cells. Finally, inducing a CTL response against HIV in vivo as described in Example 4 is not adequate to treat or prevent HIV infection. According to Weber (cited above), DNA encoding HIV proteins may induce an immune response without treating or preventing HIV. Nowhere have applicants provided any evidence that the CTL response observed is adequate to treat or prevent HIV or that the virus does not replicate too much and cause disease. As such, use of DNA encoding HIV proteins as described in Example 4 would not treat or prevent disease because the virus would replicate and cause disease and because the CTL response observed is inadequate to overcome HIV infection.

Example 9, pg 23-24, does not correlate to the claimed invention because it does not disclose delivering DNA encoding HIV proteins to the skin, inducing an immune response against the protein encoded by the DNA (GFP), or inducing a therapeutic or prophylactic immune response against HIV proteins.

'301 taught numerous HIV vectors that had decreased replication and some that induced an immune response against HIV, but '301 did not teach any HIV vectors that induced a therapeutic or prophylactic immune response against HIV or any HIV vectors that had enough infectivity/replication to induce a therapeutic immune response against HIV without causing HIV syndrome. Thus, it was unknown how to use an HIV vector to obtain a therapeutic or prophylactic immune response against HIV in a host.

The specification does not provide adequate guidance regarding how to obtain a therapeutic or prophylactic effect by applying DNA encoding a replication defective retrovirus in an animal. The specification does not teach the amount of a cellular immune response that is therapeutic or prophylactic effect against a replication defective retrovirus. The amount of dendritic cells required to obtain adequate antigen presentation is not provided in the specification. The amount of retroviral protein expression required to obtain the desired cellular immune response is not provided in the specification. The amount of replication and infectiousness required to obtain the desired balance between therapy and pathogenicity is not provided in the specification. Given the teachings in the specification taken with the unpredictability in the art at the time of filing, it would have required one of skill in the art at the time of filing undue experimentation to determine how to make and/or use a replication defective retrovirus to obtain a therapeutic/prophylactic effect without causing disease or death.

In addition, it was unpredictable what vector, promoter, dosage, cells, level of expression and route of administration would provide a therapeutic or prophylactic effect using *in vivo* or *ex vivo* gene therapy (Miller 1995, FASEB J., Vol. 9, pg 190-199; pg

198, col. 1; Deonarain, 1998, Expert Opin. Ther. Pat., Vol. 8, pg 53-69; pg 53, 1st ¶, pg 65, 1st ¶ under Conclusion section; Verma, Sept. 1997, Nature, Vol. 389, pg 239-242; see entire article, specifically pg 240, sentence bridging col. 2 and 3; Crystal, 1995, Science, Vol. 270, pg 404-410, pg 409; Ross, Sept. 1996, Human Gene Therapy, Vol. 7, pg 1781-1790; pg 1782, col. 2, 1st full ¶; pg 1789, col. 1, 1st ¶, all of record).

The specification does not enable applying DNA encoding a lentiviral protein to the skin or mucosa to transfect APCs and obtain a therapeutic or prophylactic effect. The specification does not teach applying DNA to the mucosa results transfection of APCs or in expression of the protein in the APCs. The specification does not teach the amount of lentiviral protein expression required for the APCs to present adequate antigens to the immune system such that a therapeutic/prophylactic immune response is obtained. The specification does not teach the immune response to a lentiviral antigen required to treat or prevent disease. The specification does not provide the combination of vector, promoter, dosage, level of expression that would result in a therapeutic/prophylactic effect. Given the teachings in the specification taken with the unpredictability in the art at the time of filing, it would have required one of skill in the art at the time of filing undue experimentation to determine the vector, promoter, cell, dosage, level of expression and route of administration required to obtain a therapeutic or prophylactic effect using the method claimed.

Applicants argue numerous vectors are described in the specification; therefore, applicants conclude the claims are enabled. Applicants' argument is not persuasive.

The instant application and 08/939,301 taught numerous HIV vectors that showed decreased replication and some that induced an immune response against HIV in vivo, but applicants do not teach any vectors encoding HIV proteins that induced a therapeutic or prophylactic immune response against HIV or to overcome the unpredictability in the art that the immune response obtained HIV in vivo is adequate to treat or prevent HIV.

Applicants' discussion of en re Brana is noted but is misplaced because it relates to utility and not enablement.

Applicants' discussion of the Wands factors is noted but is moot. Applicants' discussion does not set forth any error in the examiner's analysis of the claimed invention using the Wands factors in the enablement rejection.

Applicants argue the claims merely require inducing an immune response against HIV and do not require inducing an immune response against HIV that is therapeutic or prophylactic. Applicants' argument is not persuasive. Merely inducing an immune response in a mammal, in and of itself, does not have an enabled use because inducing an immune response is only described in the specification as being used to obtain a therapeutic or prophylactic effect (pg 2, lines 20-24; pg 18, lines 2-8). Therefore, inducing an immune response against HIV according to the specification must result in a therapeutic or prophylactic effect to have an enabled use. This interpretation is reasonable given the sole disclosed purpose of inducing an immune response against HIV in the specification as originally filed. Applicants have not pointed

to any other use for inducing an immune response against HIV in vivo other than therapy or prophylaxis.

Applicants' argue use of the raw material (the gene delivery complex) is enabled (pg 19, first full paragraph). Applicants' argument is not persuasive. The claims are drawn to methods of using a gene delivery complex in vivo and are not drawn to the gene delivery complex. The methods claims are rejected under enablement because the specification does not enable those of skill to use the gene delivery in vivo to obtain an immune response against HIV that is therapeutic or prophylactic.

Applicants argue publications by the inventors confirm the statement on pg 4, lines 7-11, that expression of antigens in APCs may be used to generate efficient CTL response in vivo and has the potential to generate effective vaccine and therapeutic approaches (pg 19, second full paragraph of response). Applicants' argument is not persuasive. Lisziewicz (2001) and Lisziewicz (2005) cannot be relied upon for enablement of the claims because Lisziewicz (2005) required combining DNA, PEIm and glucose, which was not disclosed in the instant application, because Lisziewicz (2001) taught a vector not described in the instant application, because neither the instant application or Lisziewicz (2005) disclosed the structure of DermaVir and because inducing an immune response against HIV as described in both references does not overcome the unpredictability in the art regarding how to induce an immune response against HIV that is therapeutic or prophylactic.

Applicants argue the specification does not have to set forth what the "prior art predicted to be needed." Applicants argue the specification taught the details of basic

research into the physiological mechanisms of the CTL response of HIV, advances in new materials, a theoretical and practical basis for targeting APCs and a method of vaccinating. Applicants' arguments are not persuasive. The specification does not teach how to perform any basic research into the physiological mechanisms of raising a CTL response against HIV. The only disclosed use for inducing a CTL response against HIV is for treatment or prophylaxis (pg 2, lines 20-24; pg 18, lines 2-8). The specification does not teach how to overcome the unpredictability in the art by teaching how to induce a CTL response against HIV in vivo that is therapeutic or prophylactic.

Applicants' argue plasmids encoding replication-defective HIV are not the same as replication-defective retrovirus particles (pg 20, first paragraph). Applicants' argument is not persuasive. While plasmids and retroviral particles encoding HIV proteins were known in the art to induce an immune response against HIV in vivo, no plasmids or retroviral particles were known in the art to induce an immune response against HIV in vivo that was therapeutic or prophylactic. Applicants have not overcome the unpredictability in the art by teaching how to obtain an immune response against HIV in vivo that is therapeutic or prophylactic.

Applicants argue Lisziewicz (2001) taught using plasmid LW/int- and refers to US application 08/803484 in Example 1 (pg 18, line 31) of the instant application. Therefore, applicants' conclude Lisziewicz (2001) correlates to the claimed invention. Applicants' argument is not persuasive. The instant application does not teach the structure of the LW/int- plasmid. While application '484 taught numerous vectors, '484 did not mention the LW/int- vector or describe any vector having six stop codons, one

deletion in the pol region, one stop codon and one deletion in the second reading frame and is integrase negative as described in Lisziewicz (2001). Therefore, the reference on pg 18, line 31, to application 08/803484 is not enabling for those of skill to make the LW/int- vector. Furthermore, Lisziewicz (2001) did not obtain a CTL response capable of treating or preventing HIV. It was known that inducing an HIV-specific immune response in vivo against HIV protein failed to provide a therapeutic or prophylactic effect (Lori and Ready, both cited above). Applicants have not provided any evidence or any reasonable explanation that the CTL response against HIV obtained in Lisziewicz (2001) overcomes such unpredictability so that a therapeutic or prophylactic effect would be obtained.

Applicants argue Lisziewicz (J. Invest. Derm.) details the use of the present invention to produce a CTL response. It is noted that Lisziewicz (2004) provided by applicants appears to be a copy of the article from the publisher. The correct citation for the article is J. Invest. Derm., Jan. 2005, Vol. 124, No. 1, pg 160-169, hereby referred to as Lisziewicz (2005).

Applicants argument is not persuasive because the specific combination of DNA, PEI-mannose and glucose described by Lisziewicz (2005) does not have support in the specification as originally filed, because the narrow limitation of applying DNA, PEI-mannose and glucose topically as described by Lisziewicz (2005) does not enable the combination of elements as broadly written and because Lisziewicz (2005) did not teach the CTL response was therapeutic or prophylactic.

Lisziewicz (2005) taught using DermaVir to make particles containing DNA, PEIm and glucose and administering the complex on about 40 cm2 skin at four locations: the left and right upper inguinal region and left and right axillary region for 30 minutes (pg 167, col. 1, "Topical and *ex vivo* DermaVir immunization"). The structure of DermaVir is described as being "formulated to make a approximately 100 nm particle containing DNA, PEIm, and glucose" (pg 167, col. 1, "Topical and *ex vivo* DermaVir Immunization" of Lisziewicz (2005)). The specific structure of DermaVir is not described. Furthermore, the combination of DNA, PEIm and glucose described by Lisziewicz (2005) does not have support in the instant specification. While the preliminary amendment contemplates using sugars, PEI, PEI derivatives or mixtures thereof (claim 23), the specification as originally filed does not contemplate the specific combination of DNA, PEI-mannose and glucose. Given the innumerable combinations of sugars, PEI and PEI derivatives, the specification as originally filed does not reasonably lead those of skill to the conclusion that applicants contemplated the specific combination of DNA, PEI-mannose and glucose as described by Lisziewicz (2005). Accordingly, the teachings of Lisziewicz (2005) cannot be relied upon for enablement.

Furthermore, Lisziewicz (2005) is limited to gene delivery particles containing plasmid DNA, PEI-mannose and glucose applied topically (pg 166, col. 2, 1st full ¶), which cannot be relied upon for enablement of the gene delivery complex described in the instant application or to applying the complex to the skin or mucosa as now claimed.

Finally, Lisziewicz (2005) induced CD4 helper and CD8 cells but did not obtain a therapeutic or prophylactic effect against HIV. However, Ready (Nature Medicine, (April

2003, Vol. 9, No. 4, pg 376) clearly states that HIV vaccines capable of preventing infections in humans was not predictable (col. 1, last full ¶) and that the road to such a vaccine "is littered with abandoned candidates" (col. 1, last 4 lines). Furthermore, obtaining a CTL response against HIV as taught in Lisziewicz (2005) is not predictive of the clinical outcome (Dong cited above). Finally, Lori (Current Medical and Chemical Anti-Infective Agents, 2004, Vol. 3, pg 31-41), one of the inventors in the instant application, taught that inducing HIV-specific antibodies failed to provide a protective effect (pg 31, col. 1, 2nd ¶, lines 7-10). Lori also says inducing a cellular immune response will not prevent HIV infection (pg 31, col. 2, first sentence of the new paragraph). While Lori suggests a cellular immune response may treat HIV in the same sentence, Lori does not teach the CTL response required to do so. Applicants have not provided any evidence or any reasonable expectation that CD4 and CD8 cells that recognize HIV proteins overcomes such unpredictability so that a therapeutic or prophylactic effect would be obtained. Without such guidance, merely inducing CD4 helper and CD8 cells that recognize HIV proteins as described by Lisziewicz (2005) is not adequate to enable inducing an immune response against HIV proteins that is therapeutic or prophylactic.

As such, Lisziewicz (2005) cannot be relied upon for enablement of the instant application because it required combining DNA, PEIm and glucose, which does not have support in the instant application, because neither the instant application or Lisziewicz (2005) disclose the structure of DermaVir and because inducing a CD4 and

CD8 response against HIV does not induce a therapeutic or prophylactic effect against HIV.

Indefiniteness

Claims 23-26, 28, 30-33, 35 and 37-43 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

Claim 23 remains indefinite because the body of the claim merely requires selecting a gene delivery complex that targets APCs and applying a complex to the skin or mucosa surface of an animal, while the preamble requires transfecting of APCs. The body of the claim never requires transfecting APCs or expressing the immunogenic protein in APCs. The preamble and the body of the claim do not have a nexus, thereby making the claim as a whole unclear. The should claim requires a clear positive step in the body of the claim indicating APCs are transfected to be commensurate in scope with the preamble of the claim. Otherwise, those of skill would not be able to determine whether transfecting APCs was an intended use (optional) or whether transfecting must occur.

Applicants' argue the claims were amended to conform to language "favored by the examiner" (pg 24 of response). Applicants' argument is unfounded. The language of the claims remains unclear. Applicants' have not provided any substantive arguments for any of the indefiniteness rejections.

Claim 23 remains indefinite because it is unclear if "transfecting" is limited to transfection with plasmid or if the term encompasses infection with a viral particle. The specification does not define "transfection". Applicants argue the term was inserted "to comply with what they thought was a demand by the examiner." Applicants do not provide any suggestions or any other arguments. Applicants' arguments are not substantive. The examiner merely rejected the previous term "transducing" under 112/2nd in the office action of 3-10-04.

Claim 23 remains indefinite because the metes and bounds of what applicants consider "applying" to the skin cannot be determined. It is unclear if the phrase is limited to putting the complex on the skin or if the phrase encompasses subcutaneous injection which results in delivery of the complex under the skin. It is unclear if intravenous injection is encompassed by the phrase because such an injection does require contact of the complex to the skin when the injection passes through the skin. Applicants previously argued the phrase had support on pg "16, line 34, where application to the skin is distinguished from injection." Applicants' argument was not persuasive. Pg 16, line 34, merely states, "The complex can be applied to the skin or mucosa surfaces directly." The citation does not discuss injection or distinguish "applying" from "injecting." Applicants' arguments do not provide any new arguments or address how to interpret the phrase. As such, one of skill would not be able to determine when they were infringing on the claim.

Claim 23 is indefinite because the phrase "gene delivery complex that targets antigen presenting cells" is unclear. It is unclear if the phrase encompasses any gene

delivery complex that transfects APCs or if the gene delivery complex has a particular structure or preference for APCs. If the gene delivery complex has a particular structure or preference for APCs, the metes and bounds of those gene delivery complexes that have a preference for transfecting APCs cannot be envisioned.

Claim 30 remains indefinite because the phrase "method of claim 28, wherein the complex comprises a 5:1 ratio of polyethylenimine derivative nitrogen per DNA phosphate" remains unclear. Claim 30 does not limit the complex to having polyethylenimine or polyethylenimine derivative; therefore, limiting the complex to having a 5:1 ratio of PEI nitrogen per DNA phosphate without first limiting the complex to one having PEI does not make sense because the complex can made with sugar (see claim 23). Furthermore, claim 30 refers to a 5:1 ratio of polyethylenimine derivative. It is unclear if applicants are attempting to limit the ratio or the compound used for gene delivery. Overall, the phrase is unclear. Applicants' have not provided any new arguments to this rejection.

Claim 31 remains indefinite because it is unclear whether the phrase "is formulated in a glucose solution" is limited to adding PEI, PEI-glu, PEI-gal, or PEI-man to a solution of glucose + water or if the phrase encompasses PEI-glu, PEI-gal, or PEI-man + water. The specification teaches PEI may be glycosylated (pg 21, Table 1) or solubilized in glucose (pg 22, line 35). Overall, it is unclear whether the phrase is limited to PEI or PEI derivative added to glucose + water or if the phrase encompasses adding PEI-glu to water. Applicants' previous arguments relating to "unexpected results" were not persuasive because they did not address the indefiniteness of the

phrase. Applicants argued both scenarios described by the examiner are encompassed by the phrase; however, PEI-glu added to water cannot be "a glucose solution" because the glucose will not solubilize in the water. Applicants' have not provided any new arguments to this rejection.

Claim Rejections - 35 USC ' 102

Claims 23-26, 28, 30-32, 35, 37, 40, 41 and 43 remain rejected under 35 U.S.C. 102(e) as being anticipated by Behr (US Patent 6,013,240, Jan. 11, 2000; 102(e) date=2-28-97) as supported by Carson (US Patent 5,679,647) for reasons of record.

Parent application 60/058,933 did not describe complexing DNA with a compound selected from the group consisting of sugars, PEI or PEI derivatives (claim 23). Therefore, claim 23 does not get priority back to parent application 60/058,933 (filed 9-15-97). Parent application 09/153,198 (filed 9-15-98) described complexing DNA with PEI-mannose in a 5-10% glucose solution on pg 26, lines 1-9. Therefore, claim 23 has priority to 9-15-98.

Behr taught a complex comprising i) PEI, and ii) plasmid DNA comprising a nucleic acid sequence encoding luciferase operatively linked to a promoter suspended in 5% glucose (col. 12, lines 53-57). Luciferase is an immunogenic protein because it is foreign to mammals and induces an immune response in mammals. Behr taught administering the complex to the skin or mucosa of an animal (claim 33, col. 6, lines 1-19). Behr taught the DNA could encode an HIV peptide (col. 3, lines 57-67). The method of Behr inherently results in transfecting APCs because dendritic cells (a type of

antigen presenting cell) are found in the epidermis (see definition of "dendritic cell", item 3). While not relied upon for the basis of the rejection, Carson provides evidence for the examiner's assertion of inherency by teaching a gene delivery complex applied to the skin transfects dendritic cells (col. 36-37, Examples 11-12). It is noted, however, the phrase "transfecting antigen presenting cells" in the preamble does not bear patentable weight in considering the art because the body of the claim does not require transfecting APCs.

Claims 25, 26 and 43 are included because they are not limited to a compound that is mannosylated PEI or PEI "from a PEI 22 kDA;" claims 25, 26 and 43 encompass non-sugar-modified PEI solubilized in glucose as in parent claim 24.

Claims 28 and 30 are included because Behr taught that between 5-20 equivalents of PEI amines are used relative to one DNA phosphate (col. 8, lines 15-19). The instant specification teaches that the ratio of 5:1 cause the complex to be electrostatically neutral (¶ bridging pg 21-22).

Claim 33 has been excluded because 5% is not "8%" as newly amended.

Claims 35 and 41 are included because administering the complex to the skin/mucosa as taught by Behr inherently would activate APCs by toxin activation. Cells would start expressing luciferase and this firefly "toxin" would be recognized as foreign by the animal, thereby activating APCs, including Langerhans cells.

Applicants argue the Examiner has erred legally because Behr does not teach all the limitations of the claims (pg 26, first full paragraph, of arguments). Applicants' argument is not persuasive because applicants do not point to one specific limitation

that Behr fails to teach. All the limitations in the claims have been addressed in the rejection.

Applicants argue the Examiner has erred factually because he uses speculation and not fact to support the fact that the luciferase protein made by an insect is inherently immunogenic as claimed (pg 26, first full paragraph, of arguments and pg 30 of arguments). Applicants' argument is not persuasive. The examiner has provided scientific reasoning that the luciferase protein would be immunogenic: because it is foreign to the animal to which the gene delivery complex is applied. Furthermore, the claims do not require inducing an immune response. Finally, Mittal (J. General Virol., Jan. 1996, Vol. 77, pg 1-9, abstract only) taught luciferase induces antibodies in rats (second to last sentence of the abstract). Luciferase must be immunogenic as claimed in any animal other than fireflies because it is a protein isolated from fireflies and because proteins isolated from one animal and introduced into another animal are recognized as foreign by the immune system and cause an immune response (Kuby, ed., Immunology, 1992, W.H. Freeman and Company, Chapter 1, "Acquired Immunity," pg 8-9). Applicants' point to the description of luciferase by bd biosciences, which states the luciferase is non-toxic. Applicants' argument is not persuasive. Toxic is defined as the quality of being poisonous, especially the degree of virulence of a toxic microbe or a poison (On-line medical dictionary definition of "toxicity"). However, the claim merely requires the protein is "immunogenic" which is defined as capable of inducing an immune response (Online Medical dictionary definition of "immunogenic").

Thus, luciferase is non-toxic but still meets the definition of an "immunogenic protein" as claimed because it induces an antibody response in animals other than fireflies.

Applicants argue Behr does not teach targeting APCs. Applicants' argument is not persuasive. The claims encompass any method that results in transfecting APCs (see 112/2nd). Carson provides evidence that the method of Behr inherently results in transfecting APCs.

Applicants argue intracerebral injection of naked DNA encoding luciferase failed to work as discussed by Behr in Example 14 (column 13, lines 9-10; pg 28 of arguments). Applicants' argument is not persuasive. The claims relate to using DNA in combination with sugars, PEI or PEI derivatives. While DNA was not successfully transferred to the brain using naked DNA, Behr successfully transferred DNA to the brain in the presence of glucose and PEI (col. 13, lines 6-10; Fig. 12). Furthermore, the claims relate to applying the gene delivery complex to the skin or mucosa, not the brain as discussed in Example 14 of Behr.

Applicants' argue the method of Carson would suffer from "low efficiency" in transfecting APCs. Applicants' argument is not persuasive. Any "efficiency" is adequate to provide evidence that the method of Behr would transfect APCs, even if it were "low." The claims do not require a particular transfection efficiency. In fact, the body of the claim does not even require transfecting APCs.

Applicants argue the advantage of the claimed invention is that is can merely be applied to the skin (pg 29 of arguments). Applicants' argument is not persuasive. Behr taught topical, cutaneous, oral, rectal, vaginal, parenteral and intranasal application (col.

6, lines 1-4), which is equivalent to applying the gene delivery complex to the skin or mucosa as claimed. The claims are not limited to topical administration of the gene delivery complex.

Applicants argue they used GFP in their experiments. Applicants' argument is not persuasive. The claims do not require the DNA encodes GFP. Applicants' arguments regarding the transgenic bunny born to express GFP are moot because the GFP is recognized as a "self" protein in the transgenic bunny; its immune system developed recognizing GFP as part of itself.

Applicants argue Carson does not provide a reasonable expectation of success because Carson used intradermal injection or a tine devise. Applicants' arguments are not persuasive. Arguments regarding an expectation of success in misplaced under 102. The teachings of Carson relate to applying the gene delivery complex to the skin using an intradermal injection or a tine devise. The claims do not exclude applying the gene delivery complex to the skin using an intradermal injection or a tine devise. The claims are not limited to applying the gene delivery complex to the skin topically.

Claim Rejections - 35 USC ' 103

Claims 23-26, 28, 30-32, 35, 37-41 and 43 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Behr (US Patent 6,013,240, Jan. 11, 2000) as supported by Carson (US Patent 5,679,647) and in view of Holler (US Patent 5,908,923) for reasons of record.

Parent application 60/058,933 (9-15-97) did not describe complexing DNA with a compound selected from the group consisting of sugars, PEI or PEI derivatives (claim 23). Parent application 09/153,198 (9-15-98) described complexing DNA with PEI-mannose in a 5-10% glucose solution on pg 26, lines 1-9; therefore, claim 23 has priority to 09/153,198 (9-15-98).

Behr taught a complex comprising i) PEI, and ii) plasmid DNA comprising a nucleic acid sequence encoding luciferase operatively linked to a promoter suspended in 5% glucose (col. 12, lines 53-57). Luciferase is an immunogenic protein because it is foreign to mammals and induces an immune response in mammals. Behr taught administering the complex to the skin or mucosa of an animal (claim 33, col. 6, lines 1-19). Behr taught the DNA could encode a peptide from HIV (col. 3, lines 57-67). The method of Behr inherently results in transfecting APCs because dendritic cells. Carson provides evidence for the examiner's assertion of inherency by teaching a gene delivery complex applied to the skin transfects dendritic cells (col. 36-37, Examples 11-12). Case law established that reliance upon inherency in an obviousness rejection (103) instead of an anticipation rejection (102) is proper. In re Skoner, et al. 186 USPQ 80 (CCPA). It is noted, however, that the phrase "transfecting antigen presenting cells" in the preamble does not bear patentable weight in considering the art because it may not occur.

Claims 25, 26 and 43 are included because they are not limited to a compound that is mannosylated PEI or PEI "from a PEI 22 kDA;" claims 25, 26 and 43 encompass non-sugar-modified PEI solubilized in glucose as in parent claim 24.

Claims 28 and 30 are included because Behr taught that between 5-20 equivalents of PEI amines are used relative to one DNA phosphate (col. 8, lines 15-19). The instant specification teaches that the ratio of 5:1 cause the complex to be electrostatically neutral (¶ bridging pg 21-22).

Claim 33 has been excluded because 5% is not "8%" as newly amended.

Claims 35 and 41 are included because administering the complex to the skin/mucosa as taught by Behr inherently would activate APCs by toxin activation. Cells would start expressing luciferase and this firefly "toxin" would be recognized as foreign by the animal, thereby activating APCs, including Langerhans cells.

Behr did not teach using a plasmid encoding a protein from a replication-defective, integrase-defective HIV.

However, Holler taught a plasmid encoding a replication-defective HIV that was integrase defective for use in vivo (col. 4, lines 51-54).

Thus, it would have been obvious for one of ordinary skill in the art at the time the invention was made to apply a gene delivery complex comprising a plasmid encoding an HIV protein to the skin/mucosa of an animal as described by Behr, wherein the plasmid encoded a replication-defective, integrase-defective HIV as taught by Holler. One of ordinary skill in the art would have been motivated to make the HIV replication-defective and integrase-defective to prevent causing disease in the animal.

The examiner acknowledges that interpreting the claims as not requiring treating or preventing HIV under 103 is different than interpreting the claims as requiring treating or preventing HIV under written description and enablement; however, both

interpretations are reasonable and all rejections have been fully supported. Assuming arguendo that the limitation of treating or preventing HIV cannot be read into the claim, the burden required to show motivation to combine Behr and Holler under obviousness is not high because the claims merely require applying a vector encoding HIV to the skin or mucosa of an animal, because Holler (and numerous other references) taught a vector encoding HIV proteins for use in vivo and because Behr suggested using a vector encoding HIV proteins in his method of transfecting in vivo.

Applicants' specific arguments about Behr and Carson have been addressed above under 102.

Applicants' arguments regarding "efficiency" have been addressed above under 102.

Applicants mention clinical trials (pg 42, "A vaccine according...") but do not correlate any clinical trial to the teachings in the specification or the claims.

Applicants argue the claims require targeting APCs. Applicants' argument is not persuasive. The method of applying a gene delivery complex to the skin or mucosa taught by Behr transfects APCs, which is equivalent to "targeting APCs" as claimed. Furthermore, Behr used DNA combined PEI which applicants clearly state is part of their invention.

Applicants argue the examiner has merely pieced together the references to come up with motivation to experiment. Applicants' argument is not persuasive. The examiner has provided a reference teaching a specific plasmid encoding a replication-

defective, integrase-defective HIV (Holler) for use in the method of Behr and motivation for why one of ordinary skill would want to combine the references. "Motivation to experiment" mischaracterizes the motivational statement provided by the examiner; the motivational statement provided by the examiner is based on the desire to prevent HIV infection or death of the animal receiving or applying a gene delivery complex. Holler provides evidence for the desire to use a replication-defective, integrase-defective HIV to induce an immune response in an animal without causing infection or death. It is noted that the claims do not require inducing an immune response against HIV or treating or preventing HIV; therefore, the burden required to combine the references for art purposes does not bear the onus of treating or preventing HIV.

Applicants argue Holler merely teaches that the replication-defective, integrase-defective HIV is usable in vivo but did not expressly use the HIV vector in vivo. Applicants' argument is not persuasive. Holler need not use the HIV vector in vivo. One of ordinary skill would have recognized from the suggestion by Holler to use the HIV vector in vivo that the method of Behr would apply because Behr suggested using his method to introduce DNA encoding HIV proteins.

The combined teachings of Behr and Holler provide a reasonable expectation of successfully transfecting cells because Holler transfected CEM (a lymphoblastoid cell line) with integrase-defective HIV. Therefore, one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of successfully transfecting APCs by applying the plasmid encoding the HIV taught by Holler to the skin or mucosa as taught by Behr.

The following prior art remains of record but not relied upon because it is pertinent to applicant's disclosure:

The proceedings of the 3rd European conference on gene therapy of cancer, held from Sept. 11-13, 1997 at the University of Berlin, as supported by Diebold (Advances in Experimental Med. and Biol., Oct. 1998, Vol. 451, pages 449-455). The preface of Advances in Experimental Med. and Biol., Oct. 1998, Vol. 451 (page v and vi) states that Vol. 451 contains the proceedings of the 3rd European conference on gene therapy of cancer. At the conference Diebold taught a complex comprising i) mannosylated PEI (PEI-man), and ii) plasmid DNA comprising a nucleic acid sequence encoding luciferase operatively linked to a promoter used to transfect dendritic cells via the mannose receptor (pg 452, line 10; pg 453, line 13-18). While Diebold described using a complex comprising PEI-man and DNA encoding an immunogenic protein at least a year and two days prior to the filing date of the instant application (Sept. 15, 1998), the conference was in Germany. 102(a) and (b) require that the information known in this country or published in this country or a foreign country prior. It does not appear that the information disclosed by Diebold was known in this country or published in any country until the publication of Advances in Experimental Med. and Biol., Vol. 451 in Oct. 1998. Therefore, the information disclosed by Diebold at the conference is not available under 102(a) or (b).

US Patent 6,420,176, application 09/153,198, claims a composition comprising DNA and mannosylated polyethylenimine, wherein said DNA encodes at least one

immunogenic protein. The composition was restricted from the "method of using" the composition in application 09/153,198.

Song (PNAS, March 1997, Vol. 94, pg 1943-1948) injected retroviral particles encoding HIV IIIB env/rev to mice intramuscularly (pg 1943, col. 2, "Retroviral vectors" and "Immunizations...") or dendritic cells transduced with the virus injected intraperitoneally (pg 1943, col. 2, "Retroviral vectors" and "Immunizations...").

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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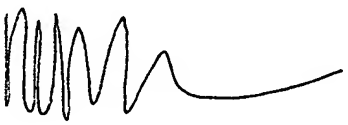
For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on 571-272-0735.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson



MICHAEL WILSON
PRIMARY EXAMINER